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**The relationship between weight gain after birth and the development of asthma in children**

Commentary on: Tsai et al. Early Life Weight Gain and Development of Childhood

Asthma in a Prospective Birth Cohort.

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The conundrum of what factors influence the high prevalence of asthma in children, particularly in developed countries, remains perplexing although most commentators are agreed that early life is likely to be an important contributor. Many observational studies in different environmental settings have reported associations between asthma in children and a whole range of early life characteristics and exposures. One factor that has received recent attention is the relationship of birth size and early postnatal growth with future respiratory health, including asthma and lung function outcomes. In this issue of the *Annals of the American Thoracic Society*, Tsai and colleagues report that faster weight gain in infants from an urban, low-income cohort in the United States was associated with a higher risk of asthma in these children after the age of two years<sup>1</sup>. The authors speculate that one explanation for this finding could be that rapid infant weight gain is also associated with an increased risk of the development of overweight and obesity in later life, thus providing a link to the well-reported obesity-asthma association, although there are still uncertainties about whether this is causal and if so what mechanisms might be responsible<sup>2</sup>.

The paper by Tsai and colleagues replicates similar observations reported in different settings, many in European populations. One of the largest of these meta-analysed results from 31 birth cohort studies comprising 147,000 children and reported that more rapid weight gain in infancy was associated with an increased risk of asthma at school age<sup>3</sup>. These results are generally consistent with other epidemiological studies<sup>4-6</sup>. The population included in the paper by Tsai and others was based on an urban population in Boston and comprised mainly low-income families with a high proportion of African Americans. Inner-city populations have received attention, particularly in the United States due to the higher prevalence of asthma reported amongst children from these communities<sup>7</sup>. Although selected for the present study for the high prevalence of both asthma and obesity in the target population, other factors have been suggested to increase asthma risk in urban cohorts, including specific allergens in the homes and exposure to high levels of atmospheric pollutants. The observation of a consistent association of early weight gain with asthma risk in a population with clearly distinct confounding structures from those in previously described populations is important. By the nature of the exposure being considered, the evidence rests on observational data, which limits the causal inferences that can be drawn from observed associations. New approaches to analysis of epidemiological data to overcome some of these historical limitations include the concept of triangulation; using data from populations in different settings, it may be assumed that similar results are unlikely to be explained by confounding, thereby strengthening the likelihood that the observed associations are real<sup>8</sup>. Therefore, accepting always that a chance relationship between two highly prevalent common childhood outcomes remains a possibility but given the consistency of these findings, what are the possible explanations for the relationship between the rate of weight gain shortly after birth and the onset of asthma during childhood?

As the authors have expounded, there are several potential mechanistic pathways that could come into play. One of these is that the exposure, in this case weight gain after birth, and outcome have common developmental origins. Size at birth is regarded as a marker of the favourability or otherwise of the intrauterine environment and consequent effects on fetal growth and wellbeing. Size at birth has been associated with an increased risk of asthma, particularly amongst infants of low birth weight (<2500grams); reviewed by Turner<sup>9</sup>. However, low birth weight includes infants that are appropriately grown but of short gestation (preterm), those that have experienced fetal growth restraint due to intrauterine adversity (intrauterine growth retardation or IUGR), and some who are healthy but small. Preterm birth has been linked to childhood wheezing disorders, including asthma<sup>3,10</sup>. Intrauterine growth retardation is associated with respiratory symptoms soon after birth and with low lung function in later childhood<sup>12</sup>, suggesting that somatic effects of a hazardous intrauterine *milieu* reflected in low birth weight have similarly deleterious effects on lung growth and development. Rapid postnatal growth has also been associated with low lung function in early life<sup>11</sup> and later childhood<sup>12</sup>. Rapid infant growth may be a marker of release from fetal growth restraint at birth and regression of weight gain to its programmed trajectory. This provides a plausible causal chain from impaired airway development to airway obstruction and respiratory symptoms in childhood leading to asthma diagnosis. It is conceivable also that deviation of fetal growth impacts the developing immune system and leads to greater allergic sensitization and manifestation of allergic diseases in childhood, although the evidence for this is scant at best<sup>13</sup>. A further possible mechanism would implicate either shared genetic pathways to obesity and asthma in later childhood or possible epigenetic effects of fetal adversity that are expressed during childhood<sup>14</sup>.

The other possibility to consider is that rapid postnatal weight gain has a direct biological effect on mechanisms leading to the development of asthma during childhood. One suggestion is that formula-feeding as opposed to breast-feeding, is associated with faster postnatal weight gain through *TORC1* signalling, which also mediates metabolic and immunologic programming resulting in a link between obesity and allergic outcomes. However, the PROBIT randomized trial of breastfeeding promotion did not show a protective effects of breastfeeding on allergic sensitization at 6 years<sup>15</sup> and the available evidence linking postnatal growth with allergy indicates a negative association<sup>13</sup>. The remaining putative mechanisms are likely to be those suggested for the link between obesity and asthma, which have been well rehearsed in the literature to date<sup>16</sup>.

In summary, this paper raises as many questions as it answers. The association between rapid postnatal weight gain and asthma does not appear to differ substantially in an urban US population from the settings in which the relationship has previously been described. The consistency of the findings suggest that this is a true observation but the mechanisms underpinning it remain to be fully explained. Rapid postnatal weight gain may be a physiological response to intrauterine events or

could be related to lifestyle and feeding practices postnatally. However, we are left with a dilemma about how to address what the authors acknowledge is an important public health problem. With the current state of knowledge, it would seem rash to suggest an intervention to attempt to regulate postnatal weight gain. Further research is certainly warranted to explore this association in more detail but whether this should be focused on specific cohorts, as in the present report, is a moot point. The finding appears to be generalisable across the target populations that have been studied in developed countries with high asthma prevalence in children. Understanding the interplay between fetal growth, size at birth and subsequent growth and how these factors influence developmental biology, including lung and immunologic structure and function will be a prerequisite to developing prevention strategies.

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